

BARRETT'S ESOPHAGUS TRANSLATIONAL RESEARCH NETWORK (BETRNet)

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Barrett's Esophagus Translational Research (BETR) Working Group Meeting

January 23-24, 2008

Chairs:

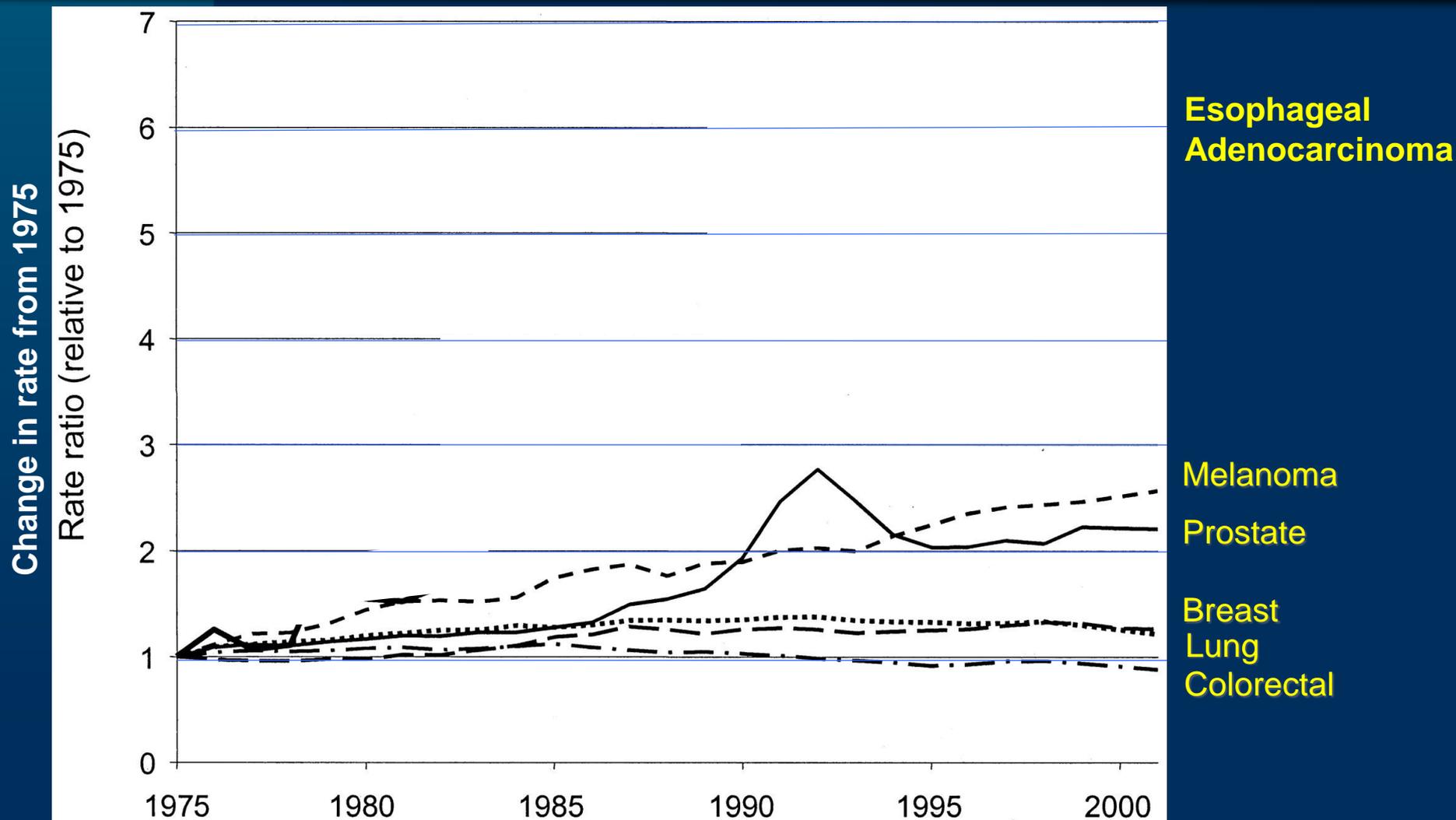
Brian J. Reid, MD, PhD

Gary Falk, MD

Unanimous recommendation:

- **Formation of a multidisciplinary, multi-institutional translational research network to lead the bench to bedside transition**
- **Accelerate the pace of BE-EA research**

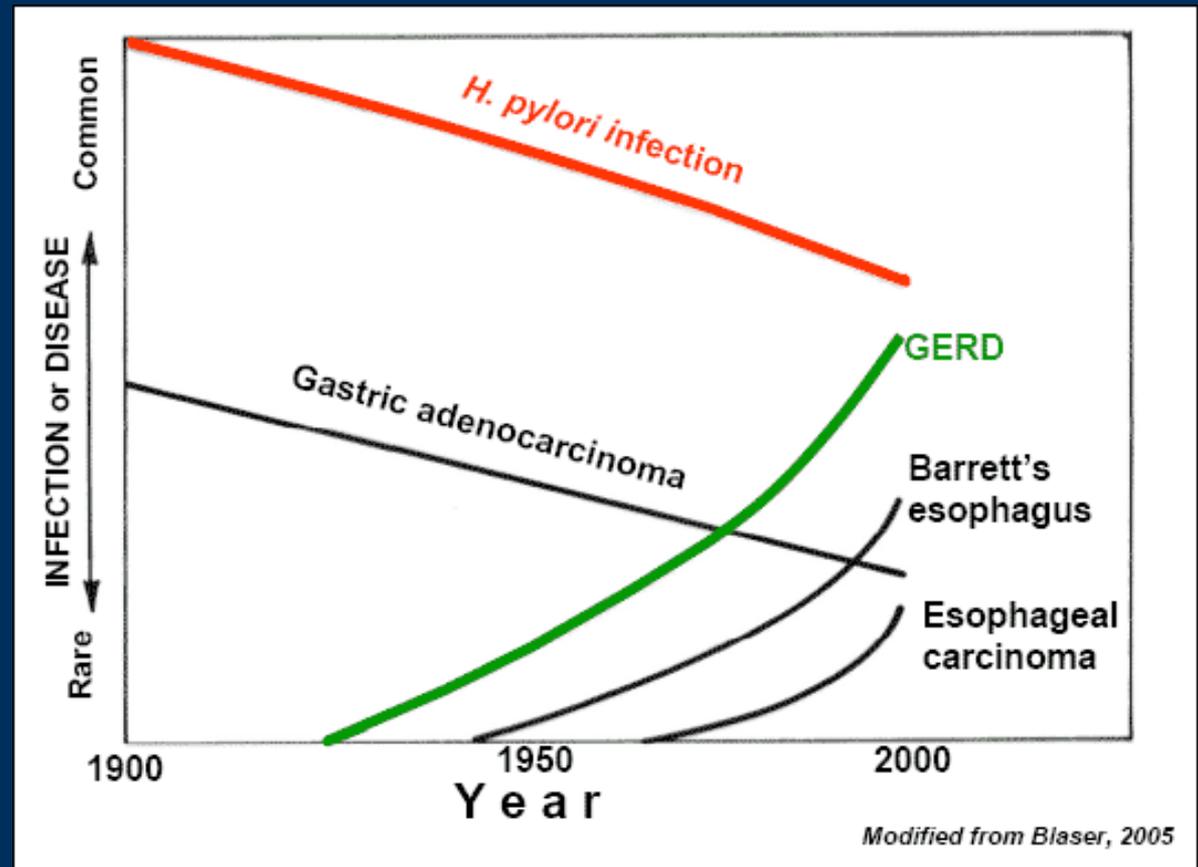
Esophageal Adenocarcinoma Incidence on the Rise



Esophageal Adenocarcinoma

Risk / Protective Factors

- GERD (Gastric Acid & Bile Reflux)
- Obesity
- Tobacco
- Diet
- NSAIDs
- H. pylori

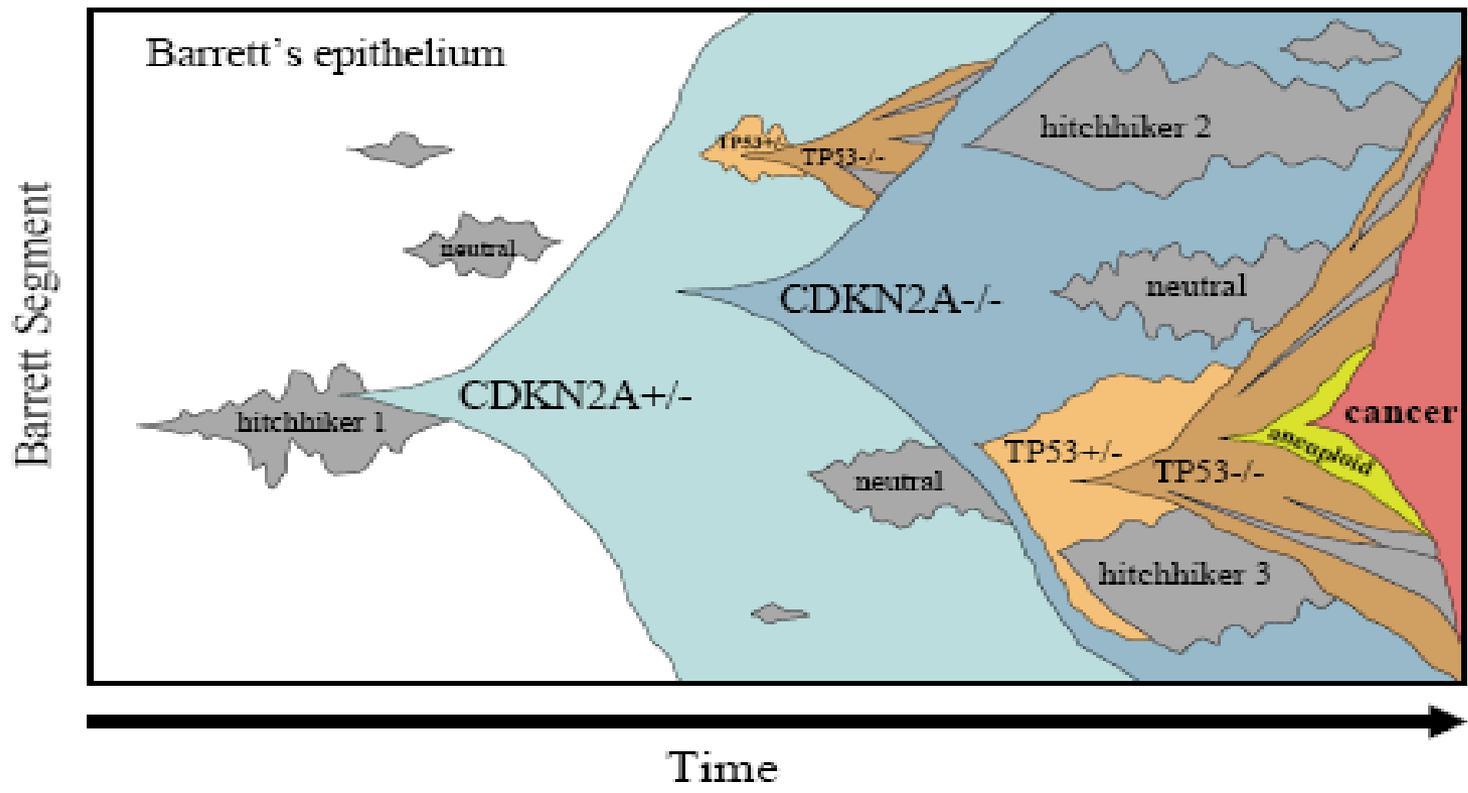


Esophageal Adenocarcinoma Carcinogenesis



Neoplastic Progression through Clonal Evolution

Neoplastic Progression in Barrett Esophagus



Mutant clones expand and drive other clones extinct within the segment

Measures of clonal diversity have been shown to be useful in predicting progression to EA

Maley 2007 Cancer Lett.

Esophageal Adenocarcinoma

Ideal Model for Carcinogenesis Research

- **A model for epithelial carcinogenesis**
- **Unique access to specimens**
 - **Serial & safe biopsies**
 - **Availability of biospecimens**
 - **Natural history**
 - **Response to intervention**
- **Motivated patients**

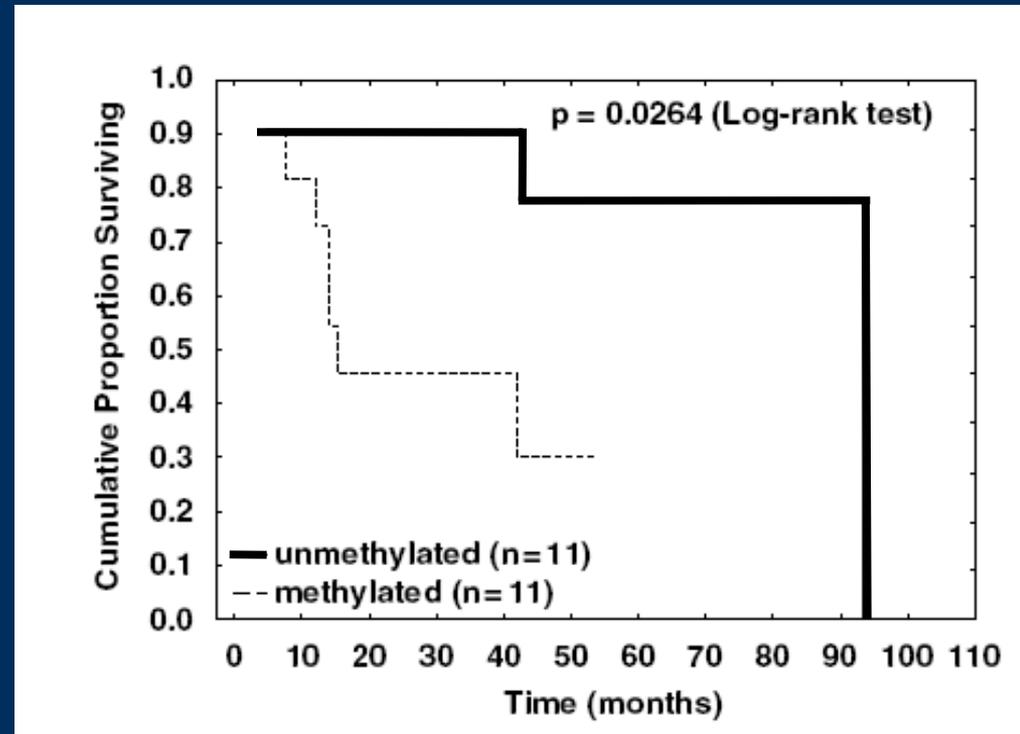
Data from these proposed multi-institutional, multi-disciplinary clinical studies must be aggregated to define statistically significant at-risk populations, risk & protective factors, natural history of EA

Esophageal Adenocarcinoma

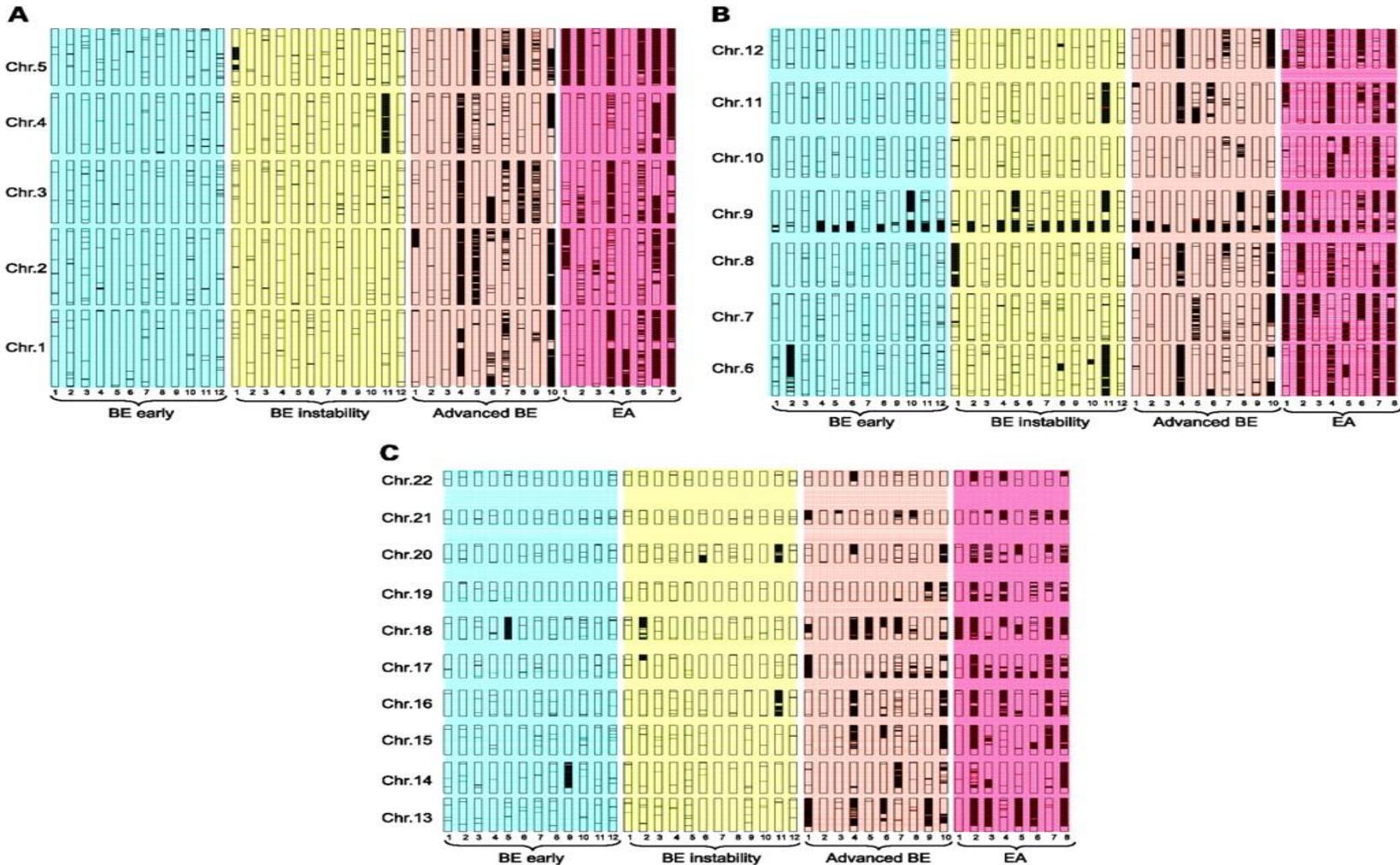
Promoter Hypermethylation of NEL-like Gene

- → gene silencing
- **Appears early in Barrett's-associated neoplastic progression**
- **Common in EA**
- **Potential biomarker of poor prognosis in early-stage EA**

Stages I–II EAC patients



Chromosomal Instability by SNP Arrays



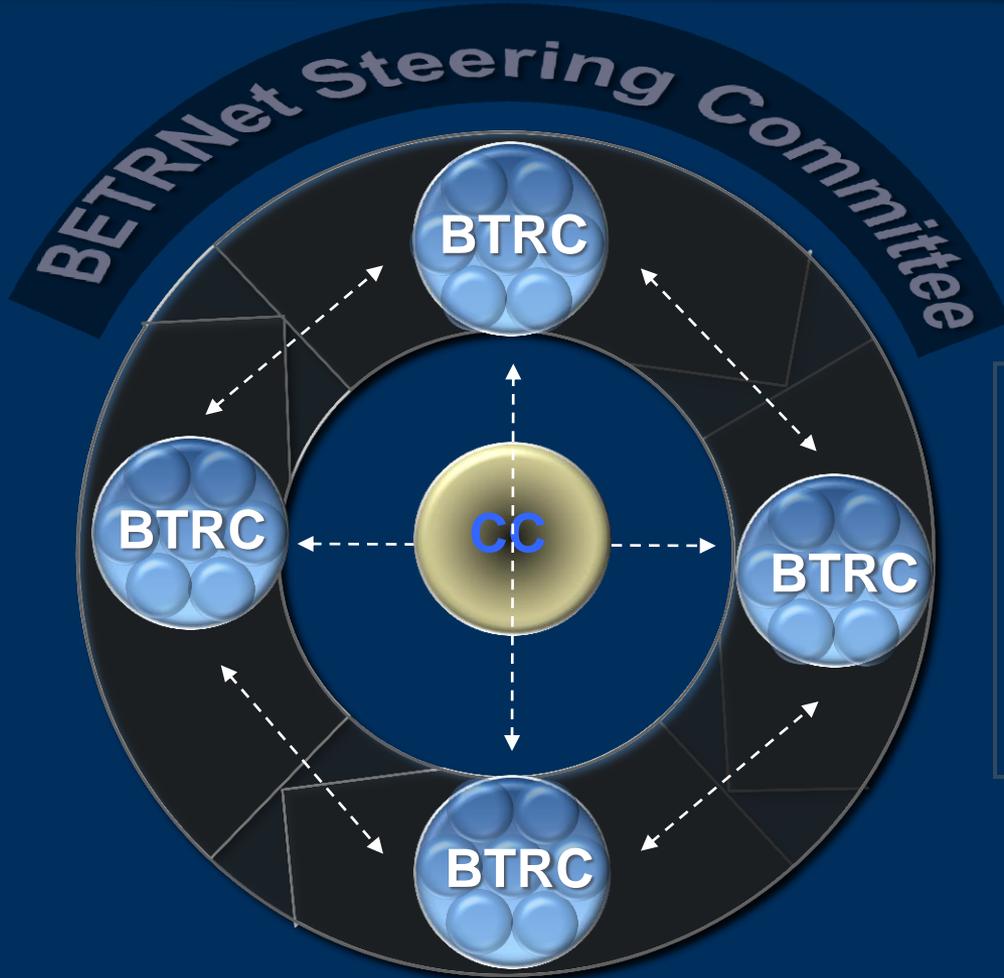
Esophageal Adenocarcinoma

Incidence, Different Baseline Abnormalities & NSAID Use

Cumulative EA incidence (# of cases)					EA Incidence/NSAID Use	
Abnormal Markers	2 y	6 y	10 y	RR (95% CI), P-value	Non-users	Users
None (n=85)	0% (0)	0% (0)	12% (3)	Baseline	1 / 25	2 / 59
One (n=104)	0.96% (1)	5.65% (5)	19.88% (8)	1.8 (0.48-6.87), >0.38	4 / 34	4 / 70
Two (n=32)	16.83% (5)	28.40 % (8)	35.56 % (9)	9.0 (2.4-33.3), <0.001	6 / 13	3 / 19
Three (n=22)	40.20 % (8)	79.12% (14)	(14)	38.7 (10.8-138.5), <0.001	10 / 12	4 / 9

BETRNet

Proposed Infrastructure



CaBIG Apps

Pt. Registry

=

BETRNet Translational Research Center = BTRC

Coordinating Center = CC

Collaborating PI

Translational Research Areas of Focus

- **Biology of EA Carcinogenesis**
 - Cell of Origin
 - Mechanisms of esophageal stem cell differentiation
 - Pathway mapping
- **Development of Novel Technologies & Models**
 - Novel preclinical models
 - Molecular profiling technologies
 - Dynamic & real-time *in vivo* imaging technologies
- **Patient Outcome-Associated Biomarkers**
 - Screening & surveillance
 - Risk assessment
 - Disease progression
 - Intervention response
- **Development & Validation of Molecularly-Targeted Interventions**

Independent Evaluation Criteria

- **Evaluation based on measurable performance criteria**
 - **Progress in BETR areas of focus**
 - **Collaboration with other NCI programs**
 - **Development of research studies within BETRNet**
 - **Participation in scientific committees**
 - **Publications**
 - **Progress reports**
 - **Development of new tools & applications for patient management**

Barrett's Esophagus / Esophageal Adenocarcinoma

Current Portfolio Analysis

- In FY 2008, NCI funded 35 projects on EA, including BE (TC: \$13,170,739)
 - Including training/small grants e.g., K, R03 & R21
- NIDDK funded 20 awards (TC: \$4,758,278); focused mainly on BE
- FY02 RFA → 50 applications
 - Funded 8 R01 (3 by NCI) 5 R21(1 by NCI)

Justification

- **Funding Mechanism**
 - **Cooperative Agreement**
- **Allows Meaningful Partnership with NCI**
 - **Steering Committee**
 - **Ensure Collaboration**
 - **Centralized Patient Registry**

Budget Request

- **\$7 Million per year for 5 years**
 - **Translational Research Centers**
 - **~\$1.5 Million for 4 Centers**
 - **Coordinating Center**
 - **\$500,000**
 - **Pilot Projects Funds**
 - **\$500,000**